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L3           1 S L2
L4          36 S L2 SSS FUL

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L5          28 S L4
L6         ANALYZE L5 1- RN HIT :      37 TERMS

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L9          24 S L5 NOT L8
L10          0 S L9 AND 2003/SO
L11          1 S L9 AND 2002/SO
L12          3 S L9 AND 2001/SO
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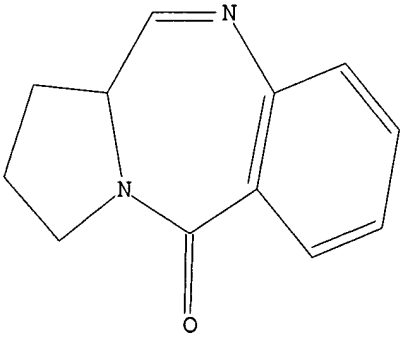

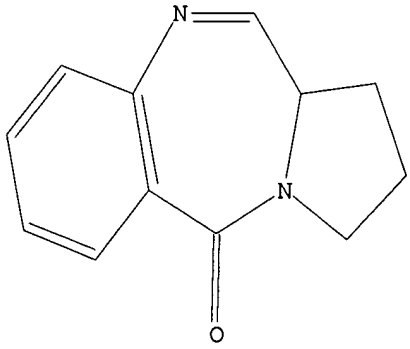


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Structure attributes must be viewed using STN Express query preparation.
L2              QUE  ABB=ON  PLU=ON  L1


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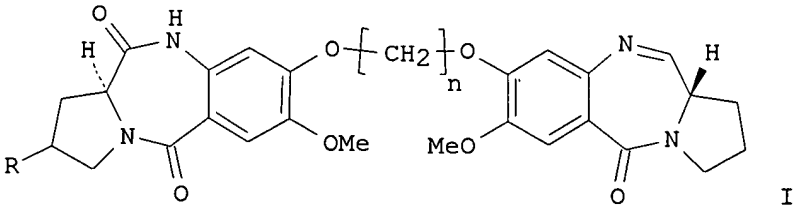
L4 ANSWER 1 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 2002:237375 CAPLUS
DN 136:263030
TI Preparation of pyrrolobenzodiazepines as antitumor agents
IN Kamal, Ahmed; Nallan, Chakravarthy Laxman; Gujjar, Ramesh; Poddutoori, Ramulu; Olepu, Srinivas
PA Council of Scientific and Industrial Research, India
SO U.S., 12 pp.
CODEN: USXXAM
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6362331	B1	20020326	US 2001-822782	20010330

PRAI US 2001-822782 20010330
OS CASREACT 136:263030; MARPAT 136:263030
GI



I

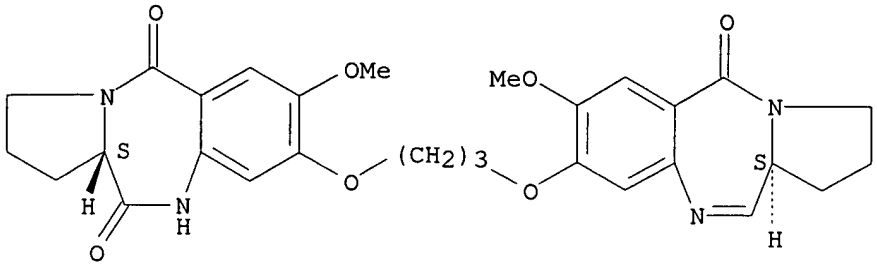
AB The present invention provides a process for the prepn. of a novel pyrrolo[2,1-c][1,4]benzodiazepine of formula I [R = H, OH, OAc; n = 3-5], by reacting (2S)-N-[4-hydroxy-5-methoxy-2-nitrobenzyl]-pyrrolidine-2-carboxaldehyde di-Et thioacetal with a dibromoalkane, isolating (2S)-N-[4-(3-bromoalkoxy)-5-methoxy-2-nitrobenzoyl]pyrrolidine-2-carboxaldehyde di-Et thioacetal so formed and reacting the isolate with a dilactam, isolating 8-{[(2S)-N-5-methoxy-2-nitrobenzoyl]pyrrolidin-2-carbaldehyde diethylthioacetal}-alkoxy-7-methoxy-2,3,5,10,11,11a-hydro-1H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dione, reducing the above nitro compd., isolating the 8-[[(2S)-N-5-methoxy-2-aminobenzoyl]pyrrolidin-2-carbaldehyde diethylthioacetal]-alkoxy-7-methoxy-2,3,5,10,11,11a-hydro-1H-pyrrolo[2,1-c][1,4]benzodiazepine-5,11-dione, reacting the amino compd. above with a deprotecting agent to obtain the pyrrolo[2,1-c][1,4]benzodiazepines. The pyrrolo[2,1-c][1,4]benzodiazepines are useful as antitumor agents. Thus, II (R = H, n = 5) was prepd. as described above and showed significant DNA binding affinity and anticancer activity against three human cell lines.

IT **343308-43-0P 343308-44-1P 343308-45-2P**
405108-10-3P 405108-11-4P 405108-12-5P
405108-13-6P 405108-14-7P 405108-15-8P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of pyrrolobenzodiazepines as antitumor agents)

RN 343308-43-0 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2,3-dihydro-7-methoxy-8-[3-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propoxy]-, (11aS)- (9CI) (CA

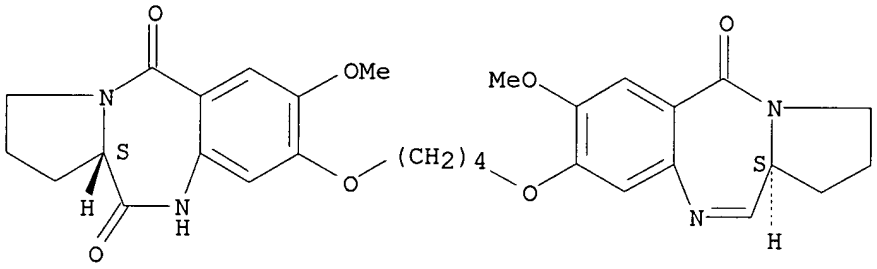
INDEX NAME)

Absolute stereochemistry. Rotation (+).



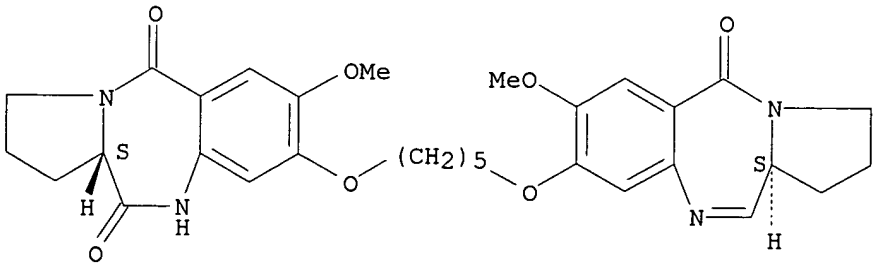
RN 343308-44-1 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2,3-dihydro-7-methoxy-8-[4-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butoxy]-, (11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 343308-45-2 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2,3-dihydro-7-methoxy-8-[[5-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]-, (11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



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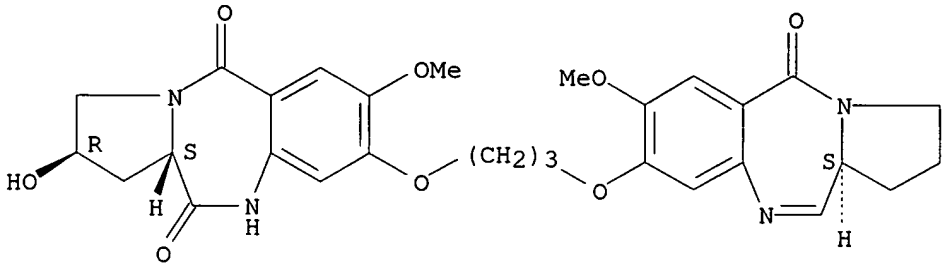
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2,3-dihydro-2-hydroxy-7-methoxy-8-[3-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propoxy]-, (2R,11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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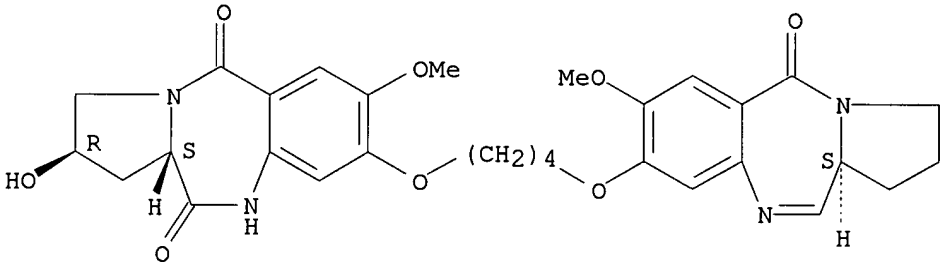
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2,3-dihydro-2-hydroxy-7-methoxy-8-[4-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butoxy]-, (2R,11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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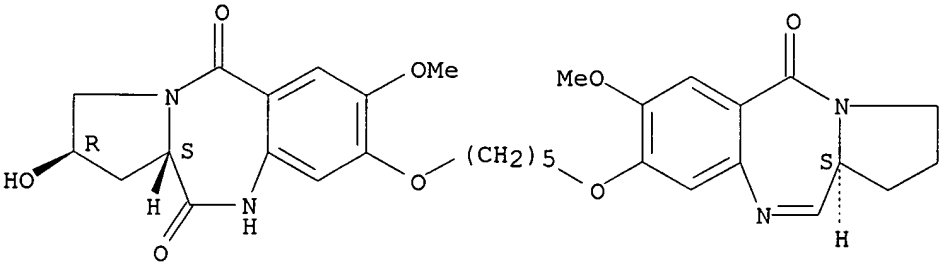
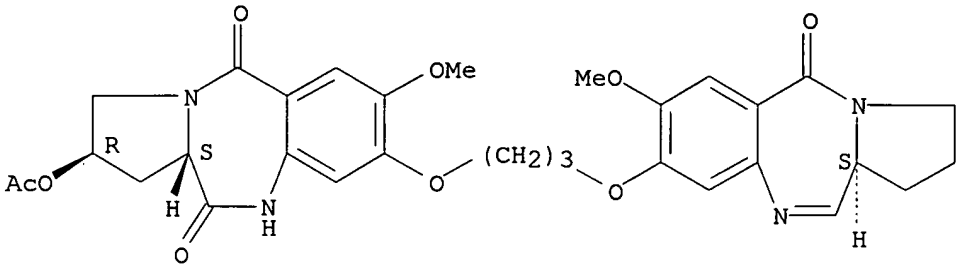
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2,3-dihydro-2-hydroxy-7-methoxy-8-[[5-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]-, (2R,11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



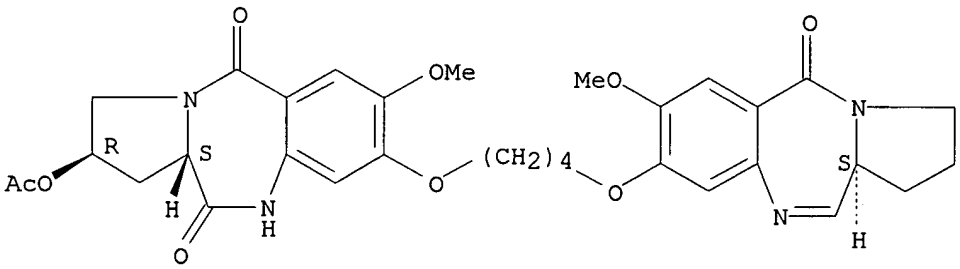
RN 405108-13-6 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2-(acetyloxy)-2,3-dihydro-7-methoxy-8-[3-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]propoxy]-, (2R,11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 405108-14-7 CAPLUS
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2-(acetyloxy)-2,3-dihydro-7-methoxy-8-[4-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]butoxy]-, (2R,11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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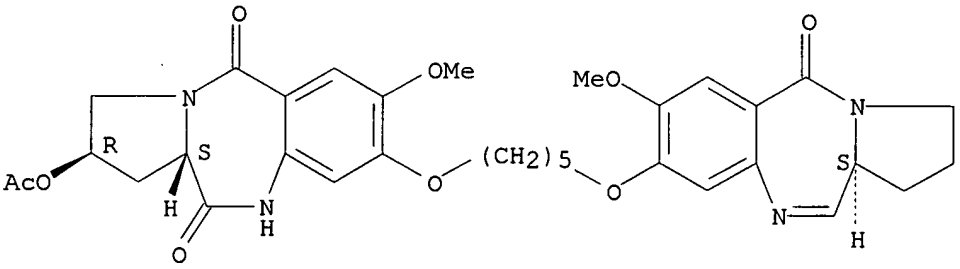
CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 2-(acetyloxy)-2,3-dihydro-7-methoxy-8-[[5-[[(11aS)-2,3,5,11a-tetrahydro-7-methoxy-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-8-yl]oxy]pentyl]oxy]-, (2R,11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

applicants

L14 ANSWER 2 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 2000:161284 CAPLUS
DN 132:207851
TI Preparation of pyrrolobenzodiazepines (PBDs) as antitumor agents
IN Thurston, David Edwin; Howard, Philip Wilson
PA The University of Portsmouth Higher Education Corporation, UK
SO PCT Int. Appl., 258 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

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	AU 9956351	A1	20000321	AU 1999-56351	19990827
	EP 1109812	A2	20010627	EP 1999-943066	19990827
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	JP 2002525285	T2	20020813	JP 2000-571054	19990827
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OS MARPAT 132:207851
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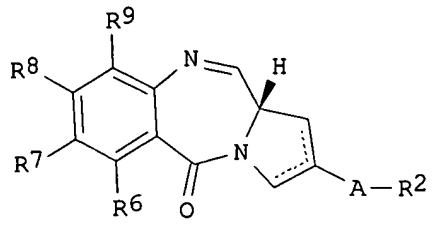

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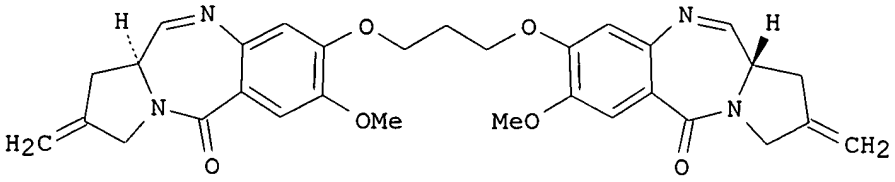


II

AB 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one derivs. (I) [wherein A = CH2 or a single bond; R = (un)substituted (ar)alkyl, (ar)alkenyl, or (ar)alkynyl; R2 = R, OH, OR, CO2H, CO2R, COH, COR, SO2R, CN; R6, R7, R8, and R9 = independently H, R, OH, OR, halo, NH2, NHR, NO2, SnMe3; or the compd. is a dimer with each monomer being the same or different and being of formula I and the R8 groups of the monomers form a -X-R'-X- bridge, where R' is an alkylene chain which may contain .gtoreq. 1 heteroatoms and/or arom. rings and/or carbon-carbon double or triple bonds, and each X = independently O, S, or N] were prepd. for the treatment of gene-based diseases, e.g. neoplastic diseases and Alzheimer's disease, and also bacterial, parasitic, and viral infections. For example, II was synthesized in a 6-step sequence. 1',3'-Bis(4-carboxy-2-methoxy-5-nitrophenoxy)propane (prepn. given) was bisamidated with (2S)-2-(tert-butyldimethylsilyloxymethyl)-4-methylenepyrrolidine (74%). TBAF-mediated cleavage of the silyl protecting groups (94%), followed by redn. of the nitro groups by NH2NH2 in the presence of Raney Ni (63%) and N-acylation with allyl chloroformate (50%), gave the protected diamine. Ring closure was accomplished under Swern oxidn. conditions, (COCl)2-DMSO and TEA, (32%). Finally, the imine was formed from the carbinolamine by N-deprotection using Pd(PPh3)4 and elimination of H2O (77%). Both large scale in vitro cytotoxicity cell screens and and in vivo hollow fiber and human tumor xenograft assays were performed on selected compds. of the invention. For instance, II exhibited potent and selective cytotoxicity against the lung cancer cell line NCI-H460, the colon cell line HCC-2998, the CNS cancer cell line SNB-75, and the melanoma cell lines MALME-3M (very potent, 0.08 .mu.M) and UACC-62 (very potent, 0.07 .mu.M). In human xenograft studies against five types of tumors, II demonstrated anticancer activity with mixed toxicity results. In addn., II was shown to be the most potent DNA-stabilizing agent known to date according to a DNA helix melting temp. assay. The IC50 value for II in the A2780 human ovarian carcinoma cell line was only 23 pM, a 320-fold increase in cytotoxicity compared to the known antitumor agent DSB-120 (IC50 = 5.2 nM). Remarkably, II was also almost 9000-fold more potent in the cisplatin-resistant A2780cisR cell line (IC50 = 24 pM) than DSB-120 (IC50 = 0.21 mM), suggesting that II may have potential in the treatment of cisplatin-refractory disease.

IT **232931-57-6P**, SJG 136

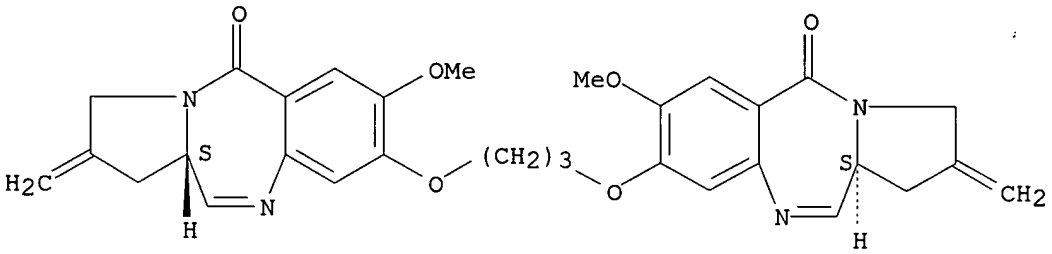
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or

effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(target compd.; prepn. of 5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one antitumor agents from 2-amino- or 2-nitrobenzoic acid derivs. and pyrrolidines)

RN 232931-57-6 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

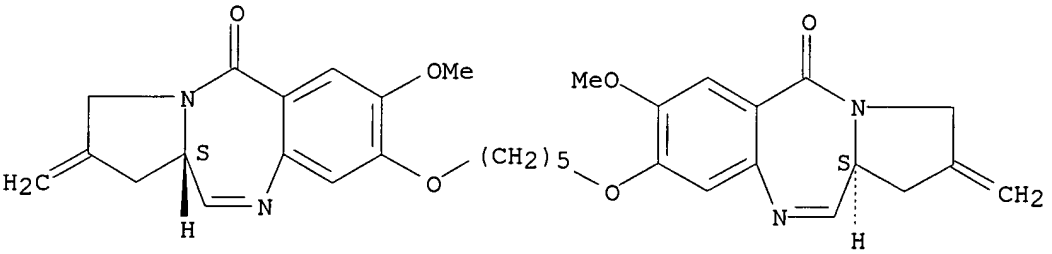


IT **260417-62-7P 260546-09-6P**, DRH 165
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(target compd.; prepn. of 5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one antitumor agents from 2-amino- or 2-nitrobenzoic acid derivs. and pyrrolidines)

RN 260417-62-7 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,5-pentanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

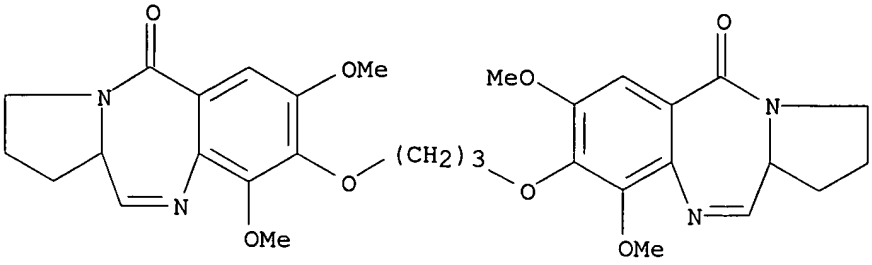
Absolute stereochemistry.



RN 260546-09-6 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7,9-dimethoxy-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L14 ANSWER 3 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 2000:161283 CAPLUS
DN 132:207703
TI Preparation of pyrrolobenzodiazepines (PBDs) as antitumor antibiotics
IN Thurston, David Edwin; Howard, Philip Wilson
PA The University of Portsmouth Higher Education Corporation, UK
SO PCT Int. Appl., 101 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

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OS MARPAT 132:207703
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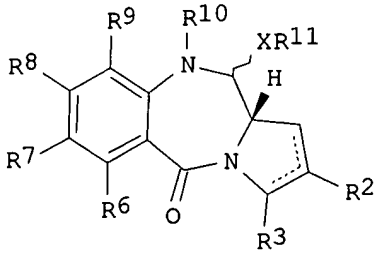
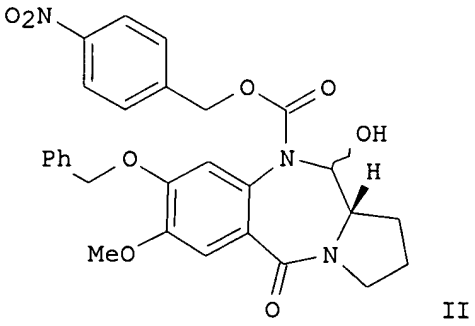


I



II

AB 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one derivs. (I) [wherein R = (un)substituted (ar)alkyl, etc.; R2 and R3 = independently H, R, OH, OR, =O, =CH-R, =CH2, CH2-CO2R, CH2-CO2H, CH2-SO2R, O-SO2-R, CO2R, COR, or CN; R6, R7, R8, and R9 = independently H, R, OH, OR, halo, NH2, NO2, or Me3Sn; or R7 and R8 together form a -O-(CH2)p-O- group, where p = 1 or 2; or the

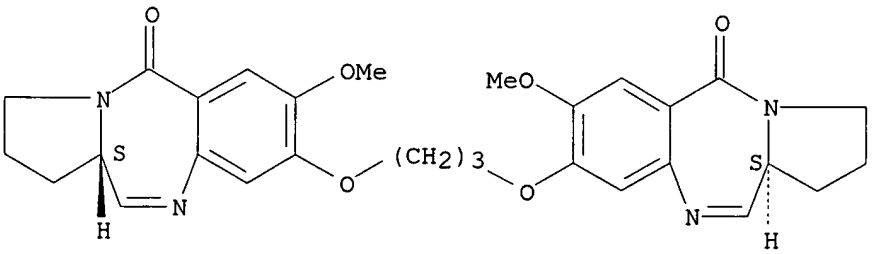
compd. is a dimer with each monomer being the same or different and being of formula I and the R8 groups of the monomers form a -T-R'-T- bridge, where R' is an alkylene chain which may contain .gtoreq. 1 heteroatoms and/or arom. rings and/or carbon-carbon double or triple bonds, and each T = independently O, S, or N; R10 = a therapeutically removable N-protecting group; R11 = H or R; X is S, O, or NH] were prepd. for the treatment of cancer and other site-specific diseases where a local increase of toxicity is beneficial to the patient. Examples include the syntheses of benzyl DC-81, benzyl tomaymycin, and DSB-120 prodrugs starting from 2-nitrobenzoic acid derivs. and pyrrolidines. Data from enzyme and light activation studies and cytotoxicity assays are also given. For example, the nitroreductase-activated benzyl DC-81 (II) was formed in a 6-step sequence involving: (1) benzylation of vanillic acid (67%); (2) ring nitration (82%); (3) amidation with (2S)-pyrrolidinemethanol (88%); (4) redn. of the nitro group (81%); (5) N-addn. of 4-nitrobenzyl chloroformate; and (6) cyclization using Swern oxidn. conditions (31%). In the presence of nitroreductase and the NADH co-factor, II demonstrated antitumor activity (IC50 = 1-5 .mu.M) against the SW1116 and LS174T human adenocarcinoma colonic cell lines. II proved non-toxic in SW1116 cells at concns. .ltoreq. 500 .mu.M and showed slight toxicity in LS174T cells at concns. > 100 .mu.M. I may also be suitable for treating bacterial, parasitic, or viral infections by exploiting a unique enzyme produced at the site of infection which is not natural to the host, or by exploiting an elevation in the amt. of an enzyme which does occur naturally in the host.

IT **140676-21-7**, DSB 120
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prepn. of pyrrolobenzodiazepinone prodrugs from 2-nitrobenzoic acid derivs. and pyrrolidines for the treatment of cancer)

RN 140676-21-7 CAPLUS

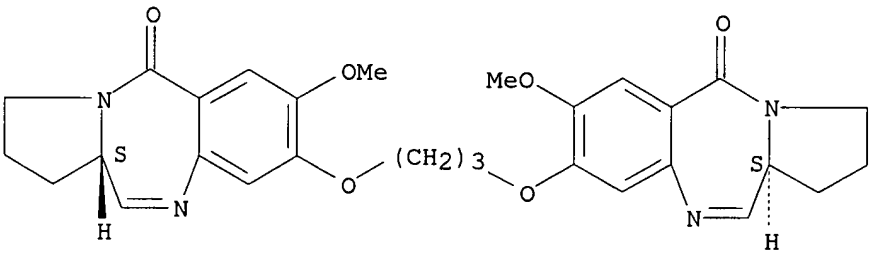
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L14 ANSWER 4 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1999:676295 CAPLUS
DN 132:18480
TI Molecular modeling of a sequence-specific DNA-binding agent based on the pyrrolo[2,1-c][1,4]benzodiazepines
AU Adams, Lesley J.; Jenkins, Terence C.; Banting, Lee; Thurston, David E.
CS CRC Gene Targeted Drug Design Research Group, School of Pharmacy and Biomedical Sciences, University of Portsmouth, Portsmouth, PO1 2DT, UK
SO Pharmacy and Pharmacology Communications (1999), 5(9), 555-560
CODEN: PPCOFN; ISSN: 1460-8081
PB Royal Pharmaceutical Society of Great Britain
DT Journal
LA English
AB The CHARMm force field was used for the first time to model the tricyclic pyrrolobenzodiazepine (PBD) ring system. This system forms the core of the well known sequence-selective DNA-interactive anthramycin-type antitumor antibiotics. The results agreed with previous results obtained using the AMBER and X-PLOR force fields. The simple family member DC-81 preferentially binds in the 5S orientation with S-stereochem. at the C11 position of the PBD and with the A-ring of the mol. oriented towards the 5' end of the covalently bound strand. The modeling studies and energetic analyses also support the observation that the mols. have a sequence preference for the purine-guanine-purine motif.
IT **140676-21-7**, DSB-120
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(mol. modeling of a sequence-specific DNA-binding agent based on the pyrrolo[2,1-c][1,4]benzodiazepines)
RN 140676-21-7 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-(9CI) (CA INDEX NAME)

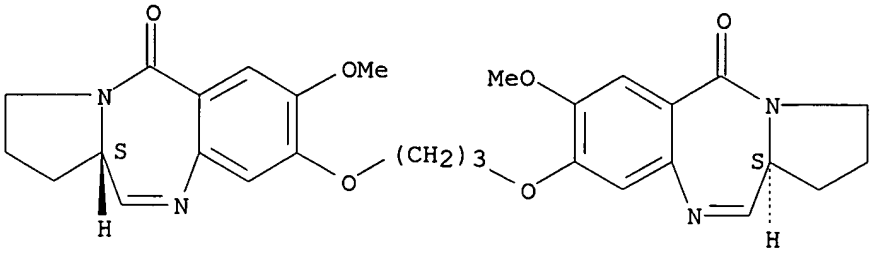
Absolute stereochemistry.



RE.CNT 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

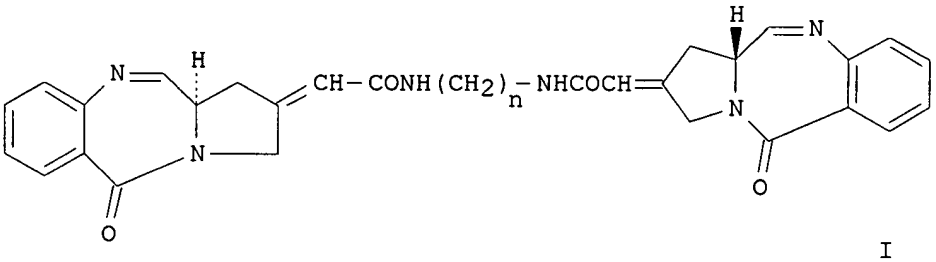
L14 ANSWER 5 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1999:583940 CAPLUS
DN 132:89603
TI Design, Synthesis, and Evaluation of a Novel Sequence-Selective Epoxide-Containing DNA Cross-Linking Agent Based on the Pyrrolo[2,1-c][1,4]benzodiazepine System
AU Wilson, Stuart C.; Howard, Philip W.; Forrow, Stephen M.; Hartley, John A.; Adams, Lesley J.; Jenkins, Terence C.; Kelland, Lloyd R.; Thurston, David E.
CS CRC Gene Targeted Drug Design Research Group School of Pharmacy and Biomedical Sciences, University of Portsmouth, Hants., PO1 2DT, UK
SO Journal of Medicinal Chemistry (1999), 42(20), 4028-4041
CODEN: JMCMAR; ISSN: 0022-2623
PB American Chemical Society
DT Journal
LA English
OS CASREACT 132:89603
AB Synthetic routes have been investigated to prep. a novel C8-epoxide-functionalized pyrrolo[2,1-c][1,4]benzodiazepine 1 as a potential sequence-selective DNA crosslinking agent (Wilson et al. Tetrahedron Lett. 1995, 36, 6333-6336). A successful synthesis was accomplished via a 10-step route involving a pro-N10-Fmoc cleavage method that should have general applicability to other pyrrolobenzodiazepine (PBD) mols. contg. acid- or nucleophile-sensitive groups. During the course of this work, a one-pot reductive cyclization procedure for the synthesis of PBD N10-C11 imines from nitro di-Me acetals was also discovered, although this method results in C11a racemization which can reduce DNA binding affinity and cytotoxicity. The target epoxide 1 was shown by thermal denaturation studies to have a significantly higher DNA-binding affinity than the parent DC-81 or the C8-propenoxy-PBD, which is structurally similar but lacks the epoxide moiety. The time course of effects upon thermal denaturation indicated a rapid initial binding phase followed by a slower phase consistent with the stepwise crosslinking of DNA obsd. for a difunctional agent. This was confirmed by an electrophoretic assay which demonstrated efficient induction of interstrand cross-links in plasmid DNA at concns. >1 .mu.M. Higher levels of interstrand crosslinking were obsd. at 24 h compared to 6 h incubation. A Taq polymerase stop assay indicated a preference for binding to guanine-rich sequences as predicted for bis-alkylation in the minor groove of DNA by epoxide and imine moieties. The pattern of stop sites could be partly rationalized by mol. modeling studies which suggested low-energy models to account for the obsd. binding behavior. The epoxide PBD 1 was shown to have significant cytotoxicity (45-60 nM) in the A2780, CH1, and CH1cisR human ovarian carcinoma cell lines and an IC50 of 0.2 .mu.M in A2780cisR. The significant activity of 1 in the cisplatin-resistant CH1cisR cell line (IC50 = 47 nM) gave a resistance factor of 0.8 compared to the parent cell line, demonstrating no cross-resistance with the major groove crosslinking agent cisplatin.
IT **140676-21-7**, DSB 120
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thermal stability with CT-DNA and in vitro cytotoxicity)
RN 140676-21-7 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



RE.CNT 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 6 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1999:444659 CAPLUS
DN 131:199684
TI Design and efficient synthesis of novel DNA interstrand crosslinking agents. C(2)-linked pyrrolo[2,1-c][1,4]benzodiazepine dimers
AU Reddy, B. S. Praveen; Damayanthi, Yalamati; Lown, J. William
CS Department Chemistry, Univ. Alberta, Edmonton, AB, T6G 2G2, Can.
SO Synlett (1999), (7), 1112-1114
CODEN: SYNLES; ISSN: 0936-5214
PB Georg Thieme Verlag
DT Journal
LA English
OS CASREACT 131:199684
GI



I

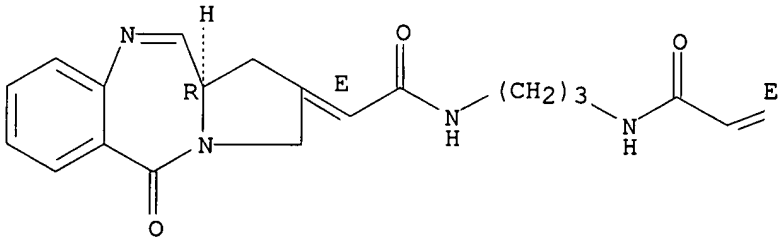
AB The design and facile synthesis of C(2)-linked pyrrolo[2,1-c][1,4]benzodiazepines I (n = 3-5) are described. The compds. are prepd. with varying degrees of linker length to probe the structural requirements for optimal DNA interstrand crosslinking. The products formed are exclusively of the E-configuration.

IT **241489-22-5P 241489-23-6P 241489-24-7P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of amide-linked pyrrolobenzodiazepine dimers)

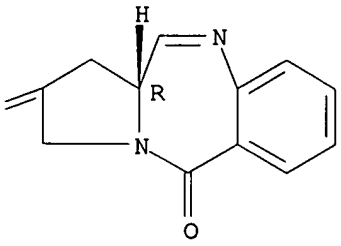
RN 241489-22-5 CAPLUS
CN Acetamide, N,N'-1,3-propanediylbis[2-[(11aR)-5,11a-dihydro-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2(3H)-ylidene]-, (2E,2'E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

PAGE 1-A



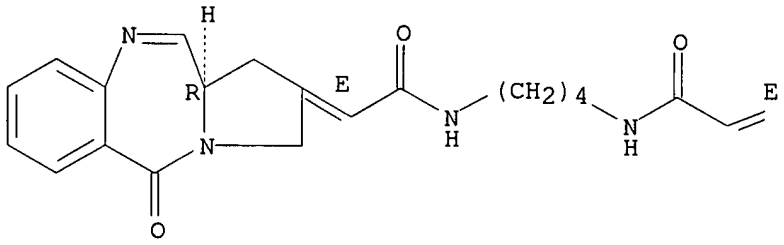
PAGE 1-B



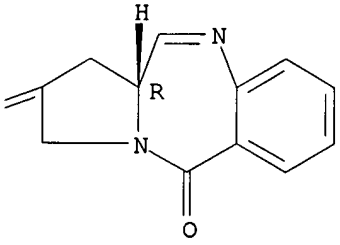
RN 241489-23-6 CAPLUS
CN Acetamide, N,N'-1,4-butanediylbis[2-[(11aR)-5,11a-dihydro-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2(3H)-ylidene]-, (2E,2'E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

PAGE 1-A



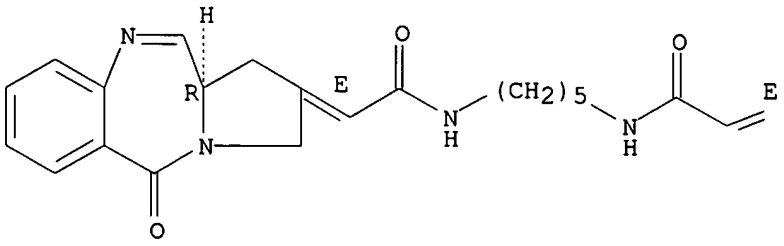
PAGE 1-B



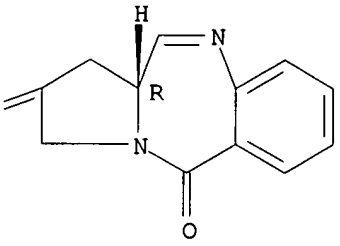
RN 241489-24-7 CAPLUS
CN Acetamide, N,N'-1,5-pentanediylbis[2-[(11aR)-5,11a-dihydro-5-oxo-1H-pyrrolo[2,1-c][1,4]benzodiazepin-2(3H)-ylidene]-, (2E,2'E)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as described by E or Z.

PAGE 1-A



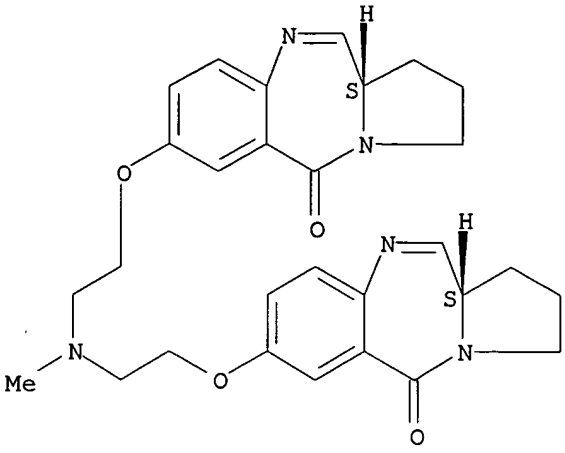
PAGE 1-B



RE.CNT 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 7 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1999:346781 CAPLUS
DN 131:140917
TI Biological effects of a bifunctional DNA cross-linker. II. Generation of micronuclei and attached micronuclear-like structures
AU Kurek, Kyle; Matsumoto, Lloyd; Gustafson, Gary; Pires, Richard; Tantravahi, Umadevi; Suggs, J. William
CS Division of Biology and Medicine, Brown University, Providence, RI, 02912, USA
SO Mutation Research (1999), 426(1), 89-94
CODEN: MUREAV; ISSN: 0027-5107
PB Elsevier Science B.V.
DT Journal
LA English
AB Madin-Darby bovine kidney (MDBK) cells were treated with the bifunctional DNA cross-linker, L-7, to examine the generation of micronuclei and other nuclear abnormalities. The preceding paper demonstrates that L-7 treatment induces the formation of triradial and quadriradial chromosomes in MDBK cells. These chromosomes are believed to result from interduplex DNA cross-links formed between G-C rich centromeric satellite DNA regions on non-sister chromatids. Treatment produces a majority of centromere-pos. micronuclei. In addn., many daughter cells remain attached by chromatin bridges which are sometimes beaded with micronuclei. Up to 15% of cell nuclei become lobular and fused with numerous micronuclear-like structures attached to their membranes. These attached structures are classified as attached micronuclear-like structures (AMNLS). Fluorescence in situ hybridization (FISH) using a centromeric satellite sequence was performed on treated cells. Hybridization reveals that intercellular bridges are composed of centromeric sequences and initiate at centromeric foci in daughter cells. Furthermore, the majority of junctions between AMNLS and nuclei contain an enhancement of centromeric signal. The frequency of AMNLS appears dependent on the concn. of L-7 and the duration of treatment. Similar results were found for the generation of cross-linked chromosome products in the previous paper. We suggest that AMNLS result from the abnormal mitotic segregation of cross-linked chromosome products.
IT **123064-64-2**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(biol. effects of bifunctional DNA cross-linker. II. Generation of micronuclei and attached micronuclear-like structures)
RN 123064-64-2 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 7,7'-[(methylimino)bis(2,1-ethanediyloxy)]bis[1,2,3,11a-tetrahydro-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

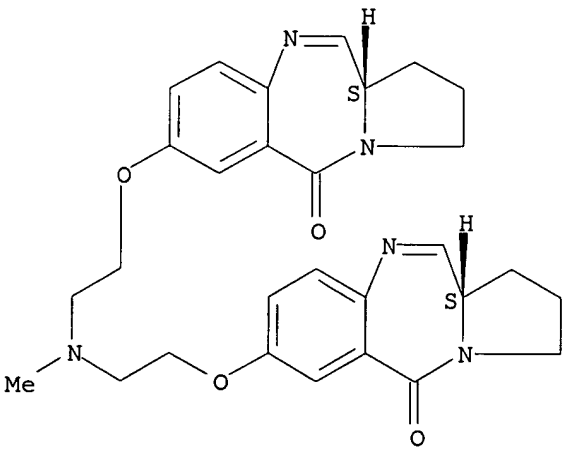
Absolute stereochemistry.



RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

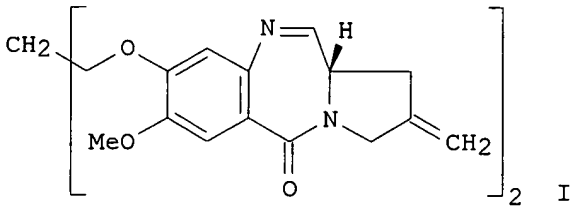
L14 ANSWER 8 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1999:346774 CAPLUS
DN 131:111396
TI Biological effects of a bifunctional DNA crosslinker. I. Generation of triradial and quadriradial chromosomes
AU Matsumoto, L.; Kurek, K.; Larocque, K.; Gustafson, G.; Pires, R.; Zhang, J.; Tantravahi, U.; Suggs, J. W.
CS Departnent of Biology, Rhode Island College, Providence, RI, 02908-1991, USA
SO Mutation Research (1999), 426(1), 79-87
CODEN: MUREAV; ISSN: 0027-5107
PB Elsevier Science B.V.
DT Journal
LA English
AB Interduplex crosslinks by a bifunctional anthramycin DNA crosslinker produced triradial and quadriradial chromosomes. The crosslinker alkylates guanine at N-2. Bovine chromosomes contain GC-rich d. satellite DNAs at the centromeric heterochromatin and is the basis for the formation of triradial and quadriradial chromosomes at the centromeres. The in situ crosslinking of interphase chromosomes indicates that the distance between centromeres is 17.5 .ANG.. We conclude that the nuclear matrix assocd. DNA in the centromeric heterochromatin of interphase chromosomes are positioned close enough for crosslinking to occur. We propose a model for the generation of triradial and quadriradial chromosomes based upon the no. of interduplex crosslinks between two chromosomes.
IT **123064-64-2**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(triradial and quadriradial chromosomes generated by the DNA-crosslinking agent L-7)
RN 123064-64-2 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 7,7'-[(methylimino)bis(2,1-ethanediyloxy)]bis[1,2,3,11a-tetrahydro-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



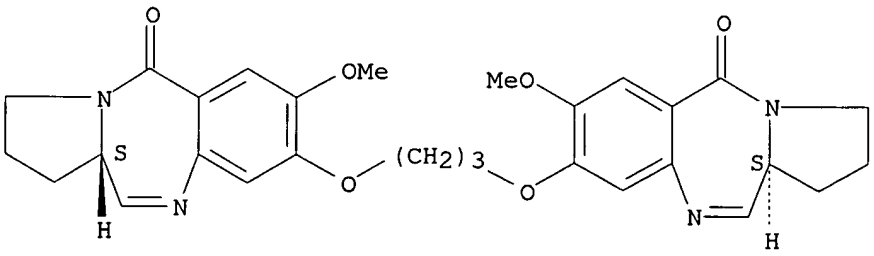
RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14 ANSWER 9 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1999:273645 CAPLUS
DN 131:116218
TI Synthesis of a novel C2/C2'-exo unsaturated pyrrolobenzodiazepine cross-linking agent with remarkable DNA binding affinity and cytotoxicity
AU Gregson, Stephen J.; Howard, Philip W.; Thurston, David E.; Jenkins, Terence C.; Kelland, Lloyd R.
CS School of Pharmacy and Biomedical Sciences, CRC Gene Targeted Drug Design Research Group, University of Portsmouth, Portsmouth, Hants, PO1 2DT, UK
SO Chemical Communications (Cambridge) (1999), (9), 797-798
CODEN: CHCOFS; ISSN: 1359-7345
PB Royal Society of Chemistry
DT Journal
LA English
GI



AB A C2/C2'-exo unsatd. pyrrolobenzodiazepine dimer (I) has been synthesized which is cytotoxic at the picomolar level and has remarkable covalent DNA binding affinity, raising the melting temp. of duplex-form calf thymus DNA by 34 after 18 h incubation.
IT **140676-21-7**, DSB-120
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(prepn. DNA binding and cytotoxicity of pyrrolobenzodiazepine crosslinking agents towards ovarian cancer cells)
RN 140676-21-7 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



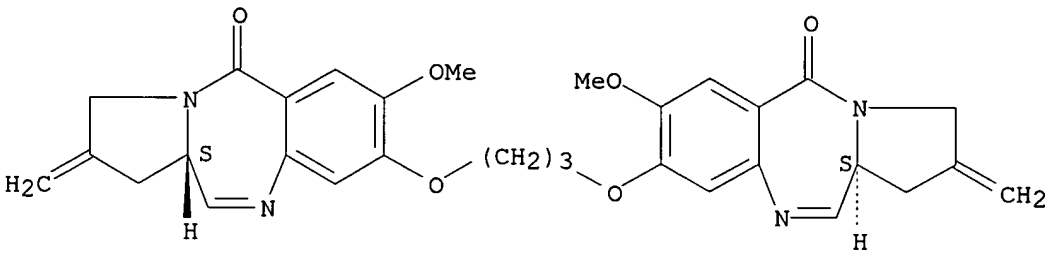
IT **232931-57-6P**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic

preparation); BIOL (Biological study); PREP (Preparation); PROC (Process)
(prepn. DNA binding and cytotoxicity of pyrrolobenzodiazepine crosslinking agents towards ovarian cancer cells)

RN 232931-57-6 CAPLUS

CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-2-methylene-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



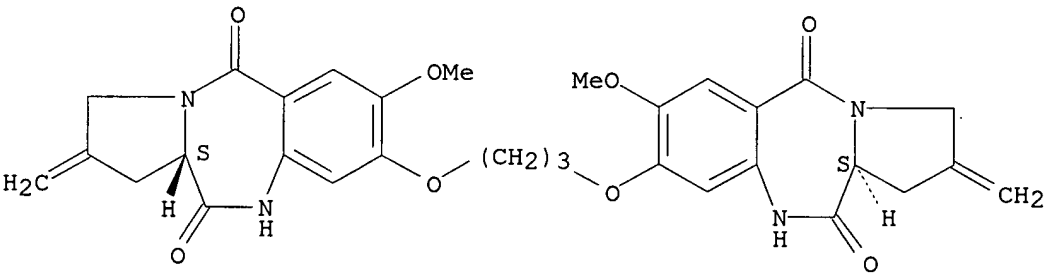
IT **232931-67-8P**

RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. DNA binding and cytotoxicity of pyrrolobenzodiazepine crosslinking agents towards ovarian cancer cells)

RN 232931-67-8 CAPLUS

CN 1H-Pyrrolo[2,1-c][1,4]benzodiazepine-5,11(10H,11aH)-dione, 8,8'-[1,3-propanediylbis(oxy)]bis[2,3-dihydro-7-methoxy-2-methylene-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

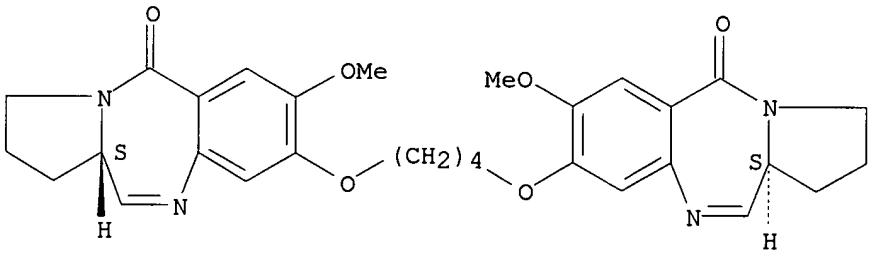
Absolute stereochemistry. Rotation (+).



RE.CNT 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

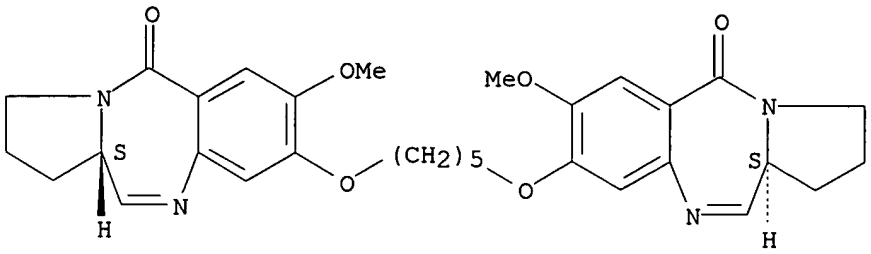
L14 ANSWER 10 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1996:644058 CAPLUS
DN 126:8088
TI Synthesis of Sequence-Selective C8-Linked Pyrrolo[2,1-c][1,4]benzodiazepine Interstrand DNA Crosslinking Agents
AU Thurston, David E.; Bose, D. Subhas; Thompson, Andrew S.; Howard, Philip W.; Leoni, Alberto; Croker, Stephen J.; Jenkins, Terrence C.; Neidle, Steven; Hartley, John A.; Hurley, Laurence H.
CS School of Pharmacy and Biomedical Science, University of Portsmouth, Portsmouth/Hants, PO1 2DT, UK
SO Journal of Organic Chemistry (1996), 61(23), 8141-8147
CODEN: JOCEAH; ISSN: 0022-3263
PB American Chemical Society
DT Journal
LA English
AB An efficient convergent synthesis of a homologous series of C8-linked pyrrolobenzodiazepine dimers with remarkable DNA interstrand crosslinking activity and potent in vitro cytotoxicity is reported. The "amino thioacetal" cyclization procedure was used to produce the electrophilic DNA-interactive N10-C11 imine moiety during the final synthetic step. In order to construct the key A-ring fragments, a versatile convergent approach has been developed to join two units of vanillic acid with .alpha.,.omega.-dihaloalkanes of varying length to provide the required bis(4-carboxy-2-methoxyphenoxy)alkanes while avoiding the formation of mixts. of monoalkylated and bisalkylated products.
IT **145325-56-0P 145325-57-1P 145325-58-2P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)
RN 145325-56-0 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-butanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



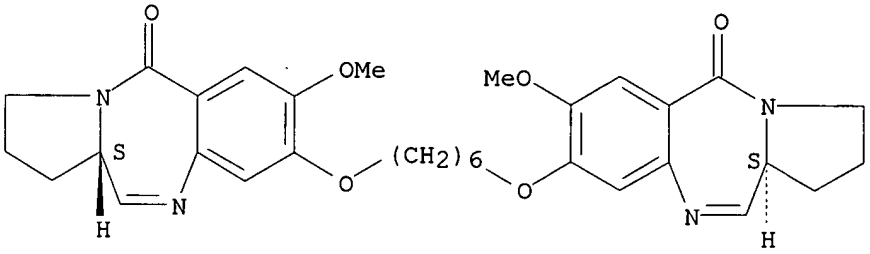
RN 145325-57-1 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,5-pentanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



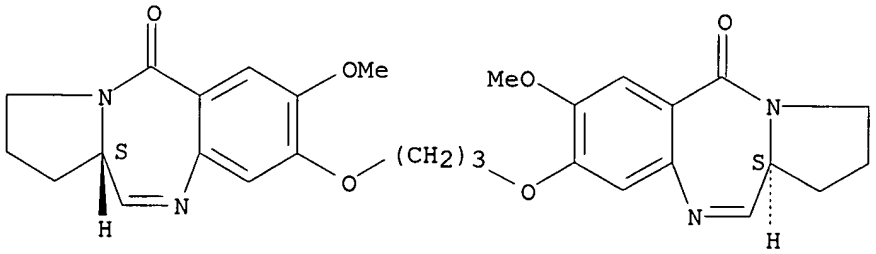
RN 145325-58-2 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,6-hexanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



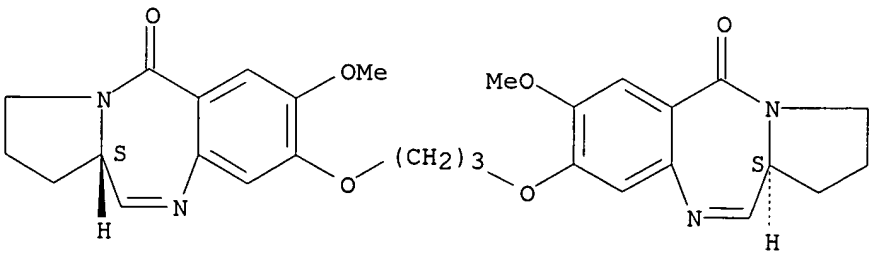
IT **140676-21-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis of sequence-selective C8-Linked pyrrolobenzodiazepine interstrand DNA crosslinking agents)
RN 140676-21-7 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

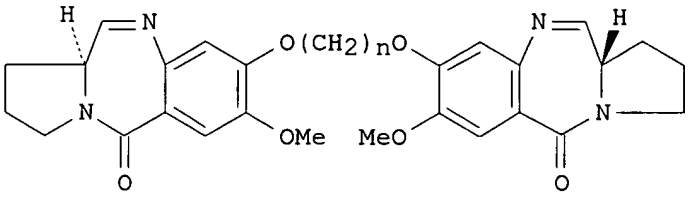


L14 ANSWER 11 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1996:550992 CAPLUS
DN 125:264974
TI Preclinical pharmacology and antitumor activity of the novel sequence-selective DNA minor-groove crosslinking agent DSB-120
AU Walton, M. I.; Goddard, P.; Kelland, L. R.; Thurston, D. E.; Harrap, K. R.
CS Institute Cancer Research, CRC Center Cancer Therapeutics, Belmont, SM2 5NG, UK
SO Cancer Chemotherapy and Pharmacology (1996), 38(5), 431-438
CODEN: CCPHDZ; ISSN: 0344-5704
PB Springer
DT Journal
LA English
AB In vitro cytotoxicity, antitumor activity, and preclin. pharmacokinetics of the novel sequence-selective, bifunctional alkylating agent DSB-120 (I), a synthetic pyrrolo[1,4][2,1-c]benzodiazepine dimer, was investigated. I was shown to be a potent cytotoxic agent against a panel of human colon carcinomas and two rodent tumors (L1210 and ADJ/PC6). The maximal antitumor effects were obsd. following a single i.v. dose but the therapeutic index was only 2.6. I was less effective when given i.p. either singly or by a daily x5 schedule. After a single i.v. dose at the max. tolerated dose the plasma elimination was biphasic, with a short distribution phase being followed by a longer elimination phase. Concns. of I in ADJ/PC6 tumors were very low, showing a peak of 0.4 .mu.gg at 5 min. The steady-state tumor/plasma ratio was about 5% and the AUC was only 2.5% of that occurring in the plasma. I appeared to be unstable in vivo, with only 1% of an administered dose being recovered unchanged in 24 h urine samples. Plasma protein binding was extensive at 96.6%. In conclusion, the poor antitumor activity of ,I may be a consequence of low tumor selectivity and drug uptake as a result of protein binding and/or extensive drug metab in vivo.
IT **140676-21-7**
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(preclin. pharmacol. and antitumor activity of DNA minor-groove crosslinking agent DSB-120)
RN 140676-21-7 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



L14 ANSWER 12 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1995:637534 CAPLUS
DN 123:285962
TI Facile and efficient synthesis of the dimers of DC-81 antitumor antibiotics
AU Kamal, Ahmed; Rao, N. Venugopal
CS Div. Org. Chem., Indian Inst. Chem. Technol., Hyderabad, 500 007, India
SO Tetrahedron Letters (1995), 36(24), 4299-302
CODEN: TELEAY; ISSN: 0040-4039
PB Elsevier
DT Journal
LA English
OS CASREACT 123:285962
GI



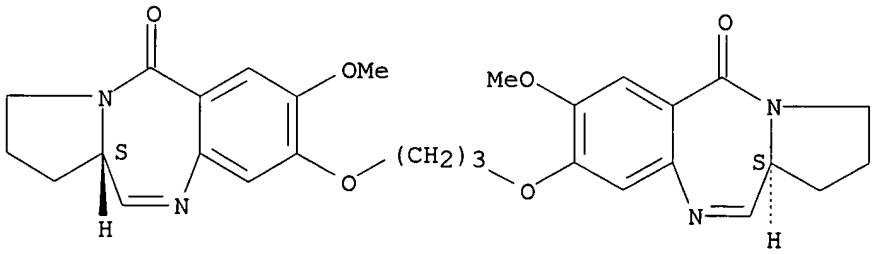
I

AB We report an improved, economical and versatile route to the dimers (I, n = 3, 4, 5) of DC-81 antitumor antibiotics. Particularly, the protection and deprotection steps in its synthesis and the prepn. of its precursors have been avoided. There is a significant improvement in the overall yields.

IT **169436-02-6P 169436-03-7P 169436-04-8P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis of the dimers of DC-81 antitumor antibiotics)

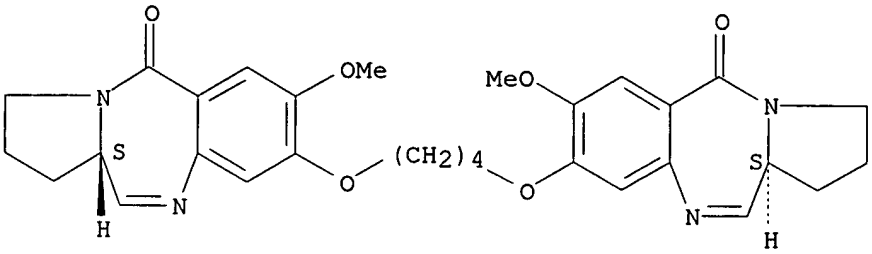
RN 169436-02-6 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (R*,R*)- (9CI) (CA INDEX NAME)

Relative stereochemistry.



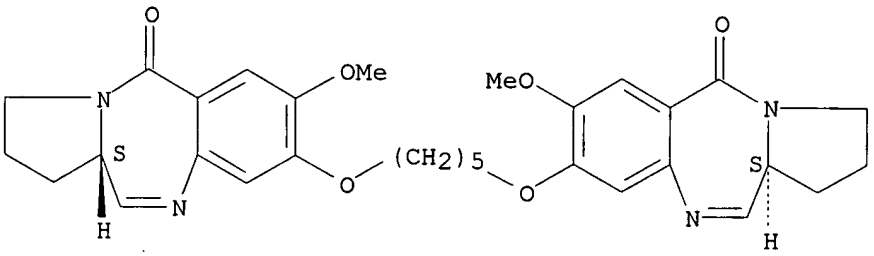
RN 169436-03-7 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-butanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (R*,R*)- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 169436-04-8 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,5-pentanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (R*,R*)- (9CI) (CA INDEX NAME)

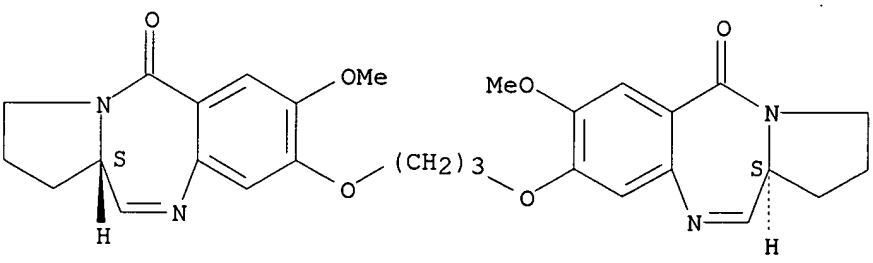
Relative stereochemistry.



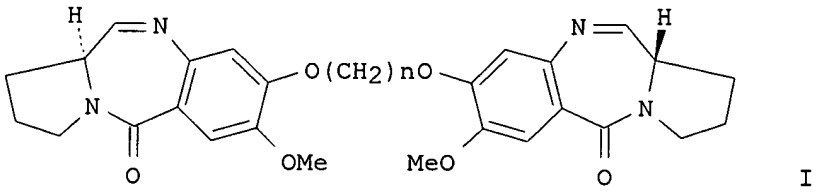
L14 ANSWER 13 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1995:107251 CAPLUS
DN 122:97894
TI DNA damage by anticancer agents and its repair: mapping in cells at the subgene level with quantitative polymerase chain reaction
AU Grimaldi, Keith A.; Bingham, John P.; Souhami, Robert L.; Hartley, John A.
CS Dep. Oncology, Univ. Coll. Long Med. Sch., London, W1P 8BT, UK
SO Analytical Biochemistry (1994), 222(1), 236-42
CODEN: ANBCA2; ISSN: 0003-2697
DT Journal
LA English
AB The quant. polymerase chain reaction (QPCR)-based assay was used to measure DNA damage and repair to a small (523 bp) fragment of the single-copy human N-ras gene in K562 cells. Compared with previous methods DNA prepn. from treated cells and the subsequent detection of the radioactive product were considerably simplified. The results demonstrated that QPCR can be used to measure damage in a small gene segment, caused by cisplatin, nitrogen, and quinacrine mustards. Drug-DNA adducts produced by two novel minor groove binding, sequence-specific mols. (AT-486 and DSB-120) could be detected at physiol. relevant concns. of drug. For both cis-platin and nitrogen mustard the concn. required to cause damage in cells were higher than those needed to cause equiv. damage in isolated DNA. In contrast both AT-488 and quinacrine mustard caused more damage at equimolar concns. in cells than in isolated DNA. DSB-120, which is closely related to AT-486, was found to be 15-fold less effective than the latter at causing damage in treated cells despite similar reactivity with isolated DNA. Repair of damage caused by quinacrine mustard to the same small gene fragment was found to proceed at a const. rate over 24 h. The QPCR assay presented here is a simple quant. method to measure damage and repair in subgene functional units such as promoters, introns, and exons.
IT **160675-00-3**, DSB 120
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(drug-DNA adducts produced by two novel minor groove binding, sequence-specific mols. (AT-486 and DSB-120) could be detected at physiol. relevant concns. of drug by quant. PCR)
RN 160675-00-3 CAPLUS

L14 ANSWER 14 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1995:50719 CAPLUS
DN 122:99738
TI Development of anthramycin-based sequence-selective DNA crosslinking agents
AU Jenkins, Terence C.; Neidle, Stephen; Thurston, David E.
CS Cancer Res. Campaign Biomolecular Structure Unit, Inst. Cancer Res., Sutton/Surrey, SM2 5NG, UK
SO Chem. Heterocycl. Compd., Proc. Symp., 11th (1993), 173-9. Editor(s): Stibor, Ivan. Publisher: Prague Inst. Chem. Technol., Prague, Czech. CODEN: 60BQAT
DT Conference
LA English
AB Mol. modeling techniques, using double-stranded DNA as a template, have been used to design a series of potent and novel DNA crosslinking agents with useful G/C recognition properties. DNA reactivity has been confirmed using biophys. and biochem. assays, and qual. structure-activity correlations for cytotoxic potency have been demonstrated. NMR soln. studies provide a rational basis for the reactivity and DNA-crosslinking efficiency of the most reactive pyrrolobenzodiazepine dimer homolog, DSB-120. The predicted d(GATC) sequence preference for this agent, where the sequence contains a spanned ApT base tract, is substantiated by facile adduct formation with d(CICGATCICG).
IT **140676-21-7**
RL: BSU (Biological study, unclassified); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent)
(pyrrolobenzodiazepine dimer homolog; development of anthramycin-based sequence-selective DNA crosslinking agents)
RN 140676-21-7 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



L14 ANSWER 15 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1994:671426 CAPLUS
DN 121:271426
TI Cellular pharmacology of novel C8-linked anthramycin-based sequence-selective DNA minor groove cross-linking agents
AU Smellie, M.; Kelland, L.R.; Thurston, D.E.; Souhami, R.L.; Hartley, J.A.
CS School, UCL Medical, London, W1P 8BT, UK
SO British Journal of Cancer (1994), 70(1), 48-53
CODEN: BJCAAI; ISSN: 0007-0920
DT Journal
LA English
GI



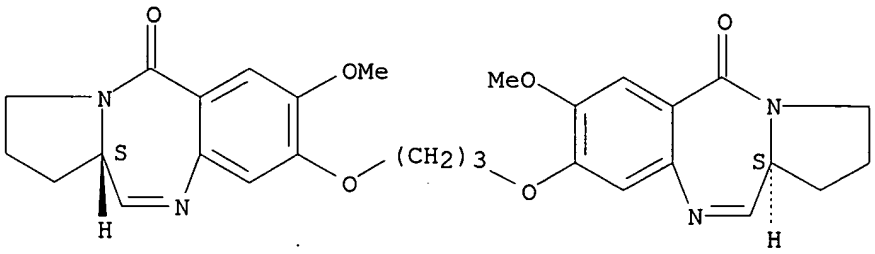
I

AB The cellular pharmacol. of a series of C8-linked pyrrolobenzodiazepine dimers with polymethylene linkers I (n = 3-6) has been studied in a range of human tumor cell lines. The four compds. showed the same pattern of relative activity in five ovarian carcinoma cell lines and one cervical carcinoma cell line, which correlated with the previously demonstrated DNA interstrand crosslinking ability of the compds. in plasmid DNA. In human leukemic K562 cells the agents produced a block in the G2/M phase of the cell cycle characteristic of crosslinking drugs, and extensive interstrand crosslinking was obsd. in cells by alk. elution with no evidence of single-strand breaks. Cross-links continued to increase up to 24 h following a 1 h exposure to drug, and no repair was evident by 48 h. In a series of ovarian and cervical carcinoma cell lines with acquired resistance to cisplatin no cross-resistance to the most potent compd. I (n = 3) was obsd. in two lines whose major mechanism of resistance to cisplatin was reduced platinum transport. Cross-resistance to 1 was obsd. in a cell line (A2780cisR) possessing elevated glutathione, and depletion of intracellular glutathione using D,L-buthionine-S,R-sulfoximine (BSO) from 10.25 nmol to 2.8 nmol 10-6 cells reduced the level of resistance from 11-fold to 2-fold compared with sensitive cells. Crosslinking in the resistant cells was restored to 80% of the level in the parent line by BSO pretreatment. There was also a correlation between glutathione levels and sensitivity to 1 measured in several other ovarian cell lines. I (n = 3) also showed cross-resistance in the doxorubicin-resistance cell line 41MdoxR and partial cross-resistance in CHldoxR cells. Both these lines possess elevated levels of p170 glycoprotein. Following treatment with 6 .mu.M verapamil, the resistance in these lines decreased almost 2-fold and 8-fold resp.

IT **140676-21-7 145325-56-0 145325-57-1 145325-58-2**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cellular pharmacol. of novel C8-linked anthramycin-based sequence-selective DNA minor groove crosslinking agents)

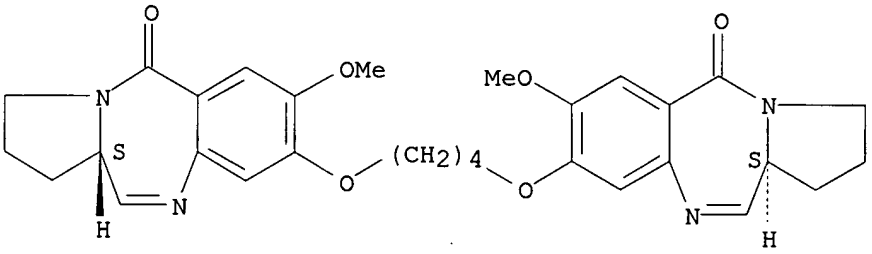
RN 140676-21-7 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



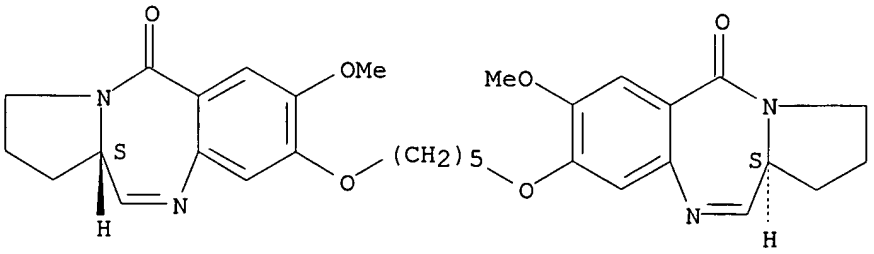
RN 145325-56-0 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-butanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



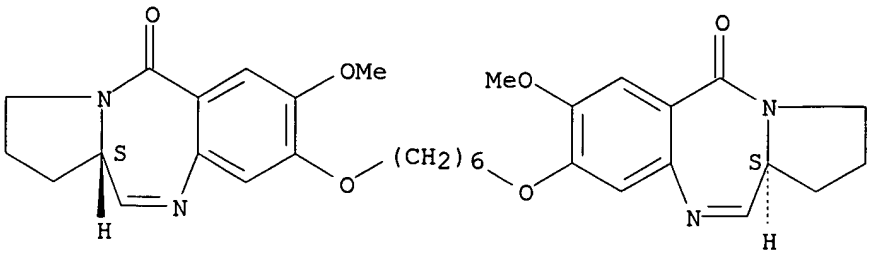
RN 145325-57-1 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,5-pentanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 145325-58-2 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,6-hexanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

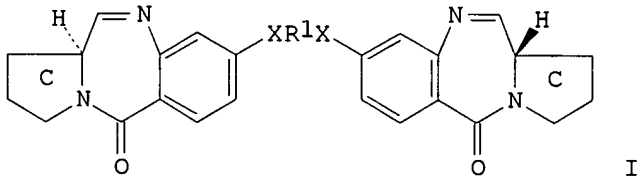
Absolute stereochemistry.



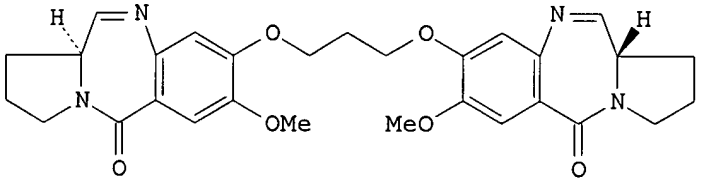
L14 ANSWER 16 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1994:270468 CAPLUS
DN 120:270468
TI Anticancer pyrrolo[2,1-c][1,4]benzodiazepines
IN Thurston, David Edwin; Bose, Deverakonda Subhas
PA Cancer Research Campaign Technology Ltd., UK
SO PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9318045	A1	19930916	WO 1993-GB483	19930308
	W: AU, CA, JP, RU, US				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	ZA 9301637	A	19931004	ZA 1993-1637	19930308
	AU 9336435	A1	19931005	AU 1993-36435	19930308
PRAI	GB 1992-5051		19920309		
	WO 1993-GB483		19930308		

OS MARPAT 120:270468
GI



I



II

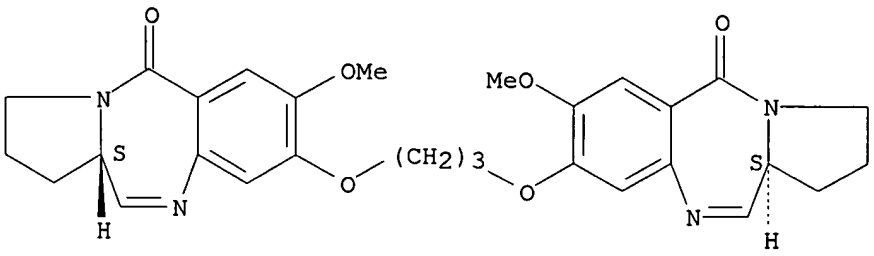
AB The title compds. I [R1 = (un)substituted C3-12 alkylene; X = O, S, NH; the pyrrolobenzodiazepine ring may contain addnl. substituents in .gtoreq.1 of the 1, 2, 3, 6, 7, 9, and 11 positions and the C rings may optionally contain .gtoreq.1 addnl. hetero ring atom], which are capable of crosslinking double-stranded DNA and which are useful as anticancer agents, are prepd. Thus, pyrrolobenzodiazepine II, prepd. from vanillic acid in 7 steps, demonstrated 50% inhibitory concn. against L1210 mouse leukemia cells of 0.01 .mu.M and against ADJ/PC6 mouse plasma plasmacytoma of 0.0005 .mu.M.

IT **140676-21-7P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. and anticancer activity of)

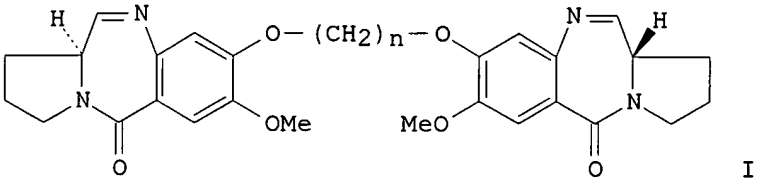
RN 140676-21-7 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-

(9CI) (CA INDEX NAME)

Absolute stereochemistry.



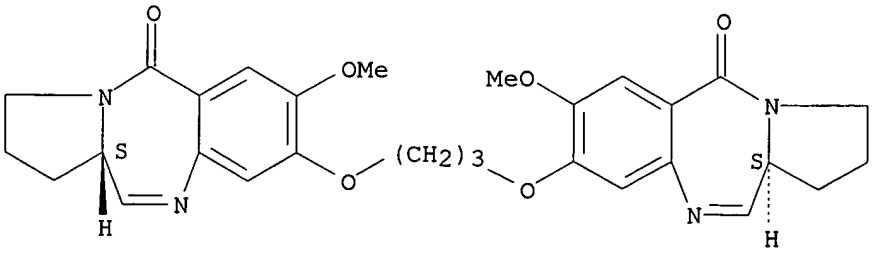
L14 ANSWER 17 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1993:59681 CAPLUS
DN 118:59681
TI Effect of linker length on DNA-binding affinity, cross-linking efficiency and cytotoxicity of C8-linked pyrrolobenzodiazepine dimers
AU Bose, D. Subhas; Thompson, Andrew S.; Smellie, Melissa; Berardini, Mark D.; Hartley, John A.; Jenkins, Terence C.; Neidle, Stephen; Thurston, David E.
CS Sch. Pharm. Biomed. Sci., Univ. Portsmouth, Portsmouth, PO1 2DZ, UK
SO Journal of the Chemical Society, Chemical Communications (1992), (20), 1518-20
CODEN: JCCCAT; ISSN: 0022-4936
DT Journal
LA English
OS CASREACT 118:59681
GI



I

AB An efficient synthesis of a homologous series of C8-linked pyrrolobenzodiazepine dimers I (n = 3-6) in 8 steps starting from vanillic acid is reported. I (n = 3, 5), with an odd no. of methylenes in the linker show a higher affinity for DNA, enhanced crosslinking efficiency, and are more cytotoxic compared with I (n = 4, 6).
IT **140676-21-7P 145325-56-0P 145325-57-1P 145325-58-2P**
RL: ADV (Adverse effect, including toxicity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. and binding with DNA and cytotoxicity of)
RN 140676-21-7 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-(9CI) (CA INDEX NAME)

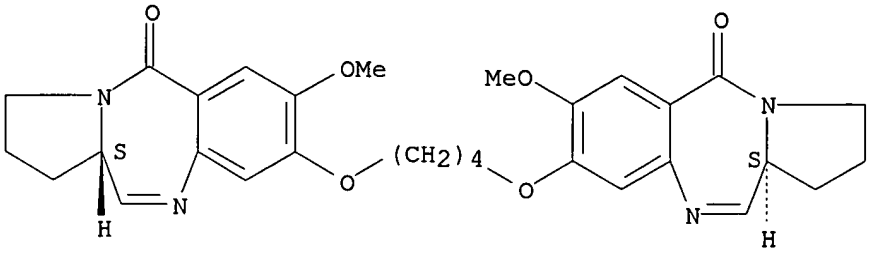
Absolute stereochemistry.



RN 145325-56-0 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,4-butanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-

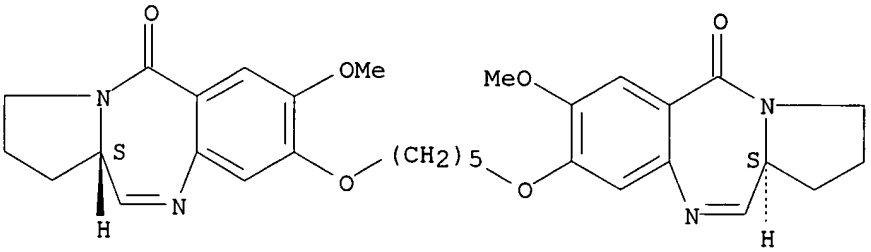
(9CI) (CA INDEX NAME)

Absolute stereochemistry.



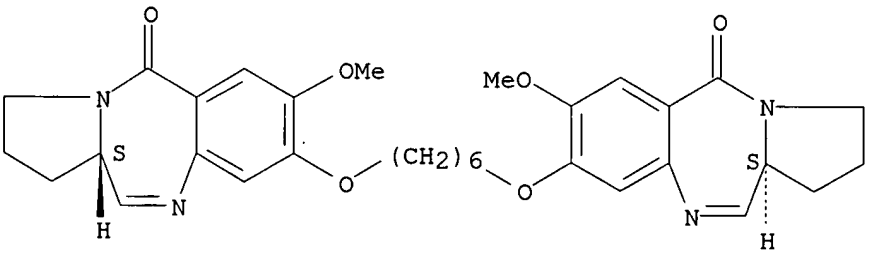
RN 145325-57-1 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,5-pentanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



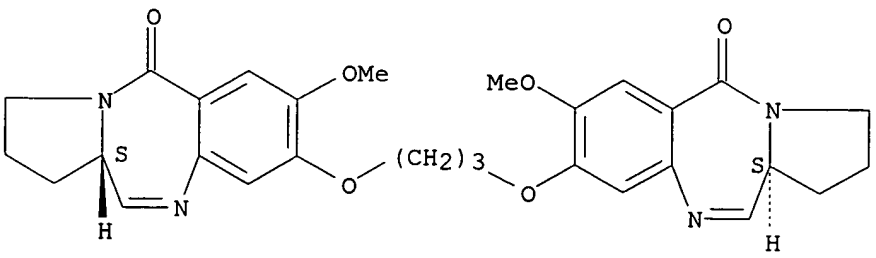
RN 145325-58-2 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,6-hexanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

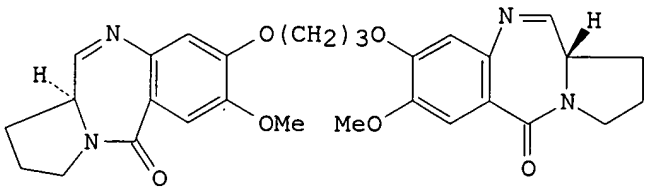


L14 ANSWER 18 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1992:483006 CAPLUS
DN 117:83006
TI Template-directed design of a DNA-DNA crosslinker based upon a bis-tomaymycin-duplex adduct
AU Wang, Jeh Jeng; Hill, G. Craig; Hurley, Laurence H.
CS Coll. Pharm., Univ. Texas, Austin, TX, 78712, USA
SO Journal of Medicinal Chemistry (1992), 35(16), 2995-3002
CODEN: JMCMAR; ISSN: 0022-2623
DT Journal
LA English
AB A template-directed approach to the design of a DNA-DNA interstrand cross-linker based upon the structure of a bis-tomaymycin-duplex adduct has been carried out. Tomaymycin is a member of the pyrrolo[1,4]benzodiazepines antitumor antibiotics. In a previous study it was shown that two tomaymycin mols. can be covalently bound to a 12-mer duplex mol., where the drug mols. are on opposite strands six base-pairs apart, and the stereochem. at the drug bonding site, and orientation in the minor groove, was defined by high-field NMR. This bis-tomaymycin 12-mer duplex adduct maintains the self-complementarity of the duplex and a B-type structure. In the present study it was shown using high-field NMR that this same 12-mer sequence can be truncated by two base pairs so that the two tomaymycin-modified guanines are now only four base-pairs apart, the two species of tomaymycin mols. are still bound with the same stereochem. and orientation, and the 10-mer duplex adduct maintains its self-complementarity. In a second 10-mer duplex it was shown that changing the bonding sequence from 5'CGA to 5'AGC does not significantly affect the structure of the bis-tomaymycin-duplex adduct. However, when the sequence is rearranged so that the drugs point in a tail-to-tail orientation rather than in the previous head-to-head configuration, there are more than one species of tomaymycin bound to DNA, and, as a consequence, the bis-tomaymycin 10-mer duplex adduct loses its self-complementarity. The 10-mer duplex contg. the 5'CGA sequence, in which the tomaymycin mols. are oriented head to head was used to design an interstrand crosslinking species in which the two drug mols. are linked together with a flexible linker mol.
IT **140676-21-7**
RL: BIOL (Biological study)
(as DNA-DNA interstand crosslinker, design of, tomaymycin-deoxyoligonucleotide adduct in relation to)
RN 140676-21-7 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



L14 ANSWER 19 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1992:255585 CAPLUS
DN 116:255585
TI Rational design of a highly efficient irreversible DNA interstrand cross-linking agent based on the pyrrolobenzodiazepine ring system
AU Bose, D. Subhas; Thompson, Andrew S.; Ching, Jingshan; Hartley, John A.; Berardini, Mark D.; Jenkins, Terence C.; Neidle, Stephen; Hurley, Laurence H.; Thurston, David E.
CS Sch. Pharm. Biomed. Sci., Portsmouth Polytech., Portsmouth, PO1 2DZ, UK
SO Journal of the American Chemical Society (1992), 114(12), 4939-41
CODEN: JACSAT; ISSN: 0002-7863
DT Journal
LA English
GI



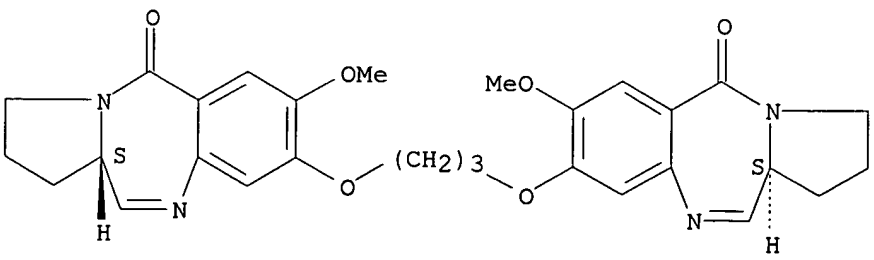
I

AB Pyrrolo[2,1-c][1,4]benzodiazepine C8 dimer DSB-120 (I) was prepd. and its DNA binding studied. I is a remarkably efficient crosslinking agent, showing activity down to at least 0.01 .mu.M and >90% crosslinking at 0.4 .mu.M. Extensive modeling studies of I with d(CGYGXXCYCG)2 show that the spatial sepn. of the pyrrolobenzodiazepine units is optimal for spanning 6 base pairs with a preference for 5'-PuGATCPy or 5'-PyGATCPu sequences, and that it actively recognizes the embedded d(GTAC)2 sequence. 1H NMR of the 1:1 adduct of I and the self-complementary 10-mer d(CICGATCICG)2 showed that the duplex is crosslinked sym. via the minor groove N2 positions of the guanines, with 11S,11S' stereochem. in the ligand, and minor distortion of the helix.

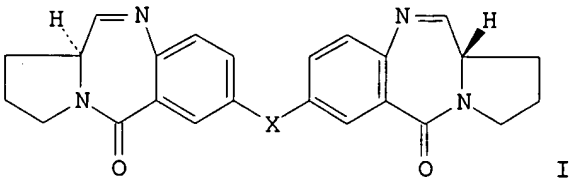
IT **140676-21-7P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn., antitumor, and DNA binding activities of)

RN 140676-21-7 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 8,8'-[1,3-propanediylbis(oxy)]bis[1,2,3,11a-tetrahydro-7-methoxy-, (11aS,11'aS)-(9CI) (CA INDEX NAME)

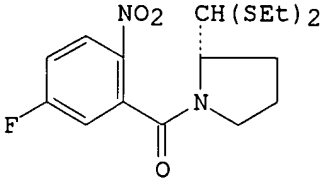
Absolute stereochemistry.



L14 ANSWER 20 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1989:573848 CAPLUS
DN 111:173848
TI Synthesis and DNA crosslinking ability of a dimeric anthramycin analog
AU Farmer, J. Dean, Jr.; Rudnicki, Suzanne M.; Suggs, J. William
CS Dep. Chem., Brown Univ., Providence, RI, 02912, USA
SO Tetrahedron Letters (1988), 29(40), 5105-8
CODEN: TELEAY; ISSN: 0040-4039
DT Journal
LA English
OS CASREACT 111:173848
GI



I



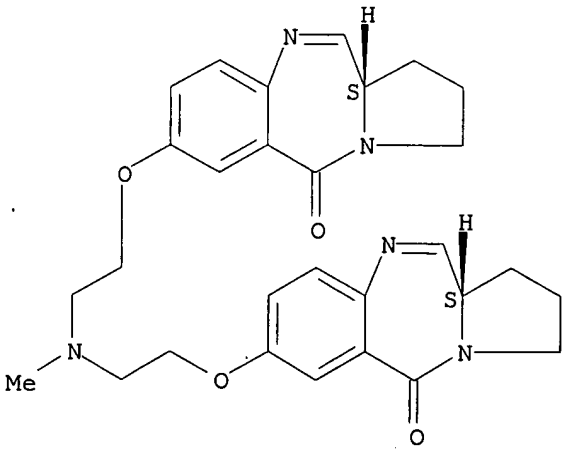
II

AB Linked analogs I [X = S(CH2)6S, OCH2CH2NMeCH2CH2O] of the DNA binding antibiotic anthramycin are made via nucleophilic arom. substitution of benzoylpyrrolidinecarboxaldehyde deriv. II followed by redn.-cyclization. The linked compds. protect DNA from restriction endonucleases and reversibly crosslink DNA.

IT **123064-64-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and DNA crosslinking by)

RN 123064-64-2 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 7,7'-[(methylimino)bis(2,1-ethanediyloxy)]bis[1,2,3,11a-tetrahydro-, (11aS,11'aS)- (9CI) (CA INDEX NAME)

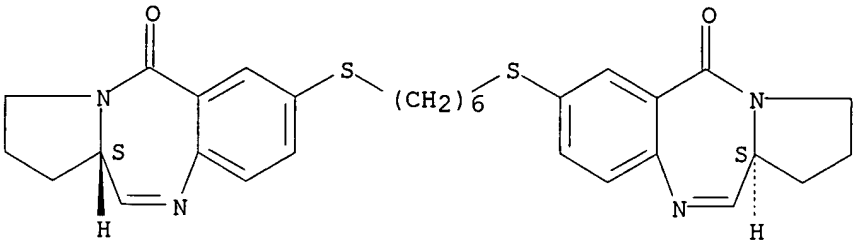
Absolute stereochemistry.



IT **123064-63-1P**

RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)
RN 123064-63-1 CAPLUS
CN 5H-Pyrrolo[2,1-c][1,4]benzodiazepin-5-one, 7,7'-[1,6-hexanediylbis(thio)]bis[1,2,3,11a-tetrahydro-, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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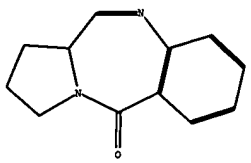
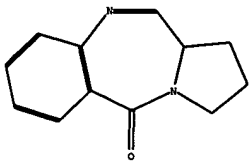
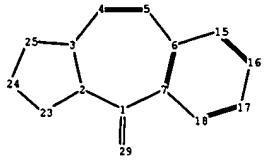
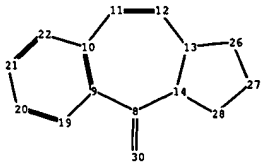

chain nodes :
29 30
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21
22 23 24 25 26 27 28
chain bonds :
1-29 8-30
ring bonds :
1-2 1-7 2-3 2-23 3-4 3-25 4-5 5-6 6-7 6-15 7-18 8-9 8-14
9-10 9-19 10-11 10-22 11-12 12-13 13-14 13-26 14-28 15-16 16-17
17-18 19-20 20-21 21-22 23-24 24-25 26-27 27-28
exact/norm bonds :
1-2 1-7 1-29 2-3 2-23 3-4 3-25 4-5 5-6 8-9 8-14 8-30 10-11
11-12 12-13 13-14 13-26 14-28 23-24 24-25 26-27 27-28
normalized bonds :
6-7 6-15 7-18 9-10 9-19 10-22 15-16 16-17 17-18 19-20 20-21
21-22

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom
10:Atom 11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:Atom
18:Atom 19:Atom 20:Atom 21:Atom 22:Atom 23:Atom 24:Atom 25:Atom
26:Atom 27:Atom 28:Atom 29:CLASS 30:CLASS